

## HUMAN SECRETED PROTEINS

### FIELD OF THE INVENTION

[0001] The present invention relates to human secreted proteins/polypeptides, and isolated nucleic acid molecules encoding said proteins/polypeptides, useful for detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating hematopoietic and hematologic diseases and disorders. Antibodies that bind these polypeptides are also encompassed by the present invention. Also encompassed by the invention are vectors, host cells, and recombinant and synthetic methods for producing said polynucleotides, polypeptides, and/or antibodies. The invention further encompasses screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further encompasses methods and compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

### BACKGROUND OF THE INVENTION

[0002] Blood is composed of a fluid component, plasma, in which are suspended red blood cells, white blood cells, and platelets. This suspension, circulating through the cardiovascular system, forms the basis of the immune system, provides all of the body's tissues with oxygen and nutrients, and removes carbon dioxide and other metabolic byproducts for excretion.

[0003] Immune cells, red blood cells, and platelets, are derived from common precursor stem cells and develop through a process known as hematopoiesis. During fetal life hematopoiesis occurs in the liver and spleen, but in the adult, hematopoiesis occurs primarily in the bone marrow and thymus. The stem cells from which all blood cells are derived proliferate and differentiate into the various blood cell lineages, (e.g., lymphoid cells (B or T cells), myeloid cells (basophils, eosinophils, neutrophils, macrophages, mast cells), thrombocytes (platelets), or erythrocytes (red blood cells)) in response to cytokines and other signals received from cells (e.g., stromal cells) in the bone marrow microenvironment. Many of the cytokines that promote the growth and differentiation of hematopoietic stem cells are known as "colony stimulating factors". For example, interleukin-3 (IL-3, and also known as multi-colony stimulating factor) and granulocyte macrophage colony stimulating factor (GM-CSF), which are released by activated macrophages and T cells, stimulate the production of macrophages and granulocytes (myelopoiesis). Stem cell factor (SCF, c-kit ligand) is a growth factor for primitive lymphoid and myeloid hematopoietic bone marrow progenitor cells expressing the early cell surface marker CD34. Other hematopoietic cytokines/growth factors include, but are not limited to macrophage colony stimulating factor (M-CSF), granulocyte colony stimulating factor (G-CSF), and erythropoietin (EPO). Interleukins-1, 6, and 7 have also been shown to function as hematopoietic growth factors/cytokines. Deficiencies in the quantities of mature red or white blood cells, either as a result of insufficient production or excessive destruction, may result in anemias and/or immunodeficiencies.

[0004] In addition to the cellular component of the blood, there are a remarkable variety of soluble blood-borne pro-

teins that serve important physiological functions. Descriptions of some of the functional classes of blood proteins, along with representative members of these classes, are given below.

#### Coagulation Factors

[0005] The formation of insoluble protein aggregates at the site of vascular injury or inflammation, termed coagulation, is the result of multiple interacting coagulation factors (Dahlback, B., *Lancet* 355:1627-32). This cascade of interdependent proteins (including Factors V, VIII, IX, X XI, and XII) results in the production of the protease, thrombin. Thrombin converts blood-soluble fibrinogen into fibrin, which polymerizes into insoluble clots that are stabilized by the activity of Factor XIII. This process is balanced by the activity of coagulation inhibitors such as antithrombin III, heparin cofactor II, Protein C and Protein S. Imbalance between pro-clotting factors and coagulation inhibitors leads to potentially serious medical conditions, including improper wound healing and the bleeding disorders hemophilia A and B, as well as excessive clotting disorders such as thrombosis (e.g. cerebral, coronary, and placental), pulmonary embolus, stroke, and coronary artery disease. For a more extensive review see Triplett, D., *Clin Chem* 46:1260-9.

#### Immunoproteins

[0006] Blood plasma contains a number of proteins that contribute to the immune response. Immunoglobulin antibodies are glycoproteins with similar structural domains, which bind to specific antigenic invaders and trigger other components of the immune system. The complement cascade, a network of about 20 interacting proteins, is activated by antigen-antibody complexes and results in the lysis of infected cells, as well as other important immune functions. Immunoproteins are important tools for the diagnosis and treatment of infection, cancer, and other disorders. For more detailed discussion of immunoproteins see Meri, J. and Jarva, H., *Vox Sang* 74 suppl. 2:291-302 and Chapter 23 of *Molecular Biology of the Cell*, 3<sup>rd</sup> Edition, edited by Alberts, B. et al.

#### Hormones

[0007] The blood serves as a major vehicle for hormones and other secreted signaling molecules that act at a site distant to their release. A number of peptide hormones function as regulators of homeostatic processes. For example, parathyroid hormone and calcitonin oppositely regulate serum levels of calcium. Blood-borne peptide hormones that regulate carbohydrate metabolism include insulin, glucagon, and adrenocorticotropin hormone. Vasopressin, angiotensin, and bradykinin are hormones that modulate vasodilation and blood pressure. Follicle-stimulating hormone and leutinizing hormone play important roles in both male and female reproductive functions. Dysfunction of these hormones can lead to a wide spectrum of disorders, including osteoporosis, diabetes, psychiatric disorders, hypoglycemia, obesity, infertility, as well as hypo- and hypertension.

#### Cytokines

[0008] Cytokines are a class of circulating proteins that act primarily as intercellular signaling molecules regulating hematopoiesis, angiogenesis, and immune system functions.